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PATENT
Attorney Docket No. **CASE-02138**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Paul V. Lehmann *et al.*
Serial No.: 08/621,725 Group No.: 1644
Filed: 03/21/96
Examiner: Ron Schwadron, Ph.D.
Entitled: **METHODS FOR INDUCING IMMUNITY**

#21
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11/29/99

APPELLANTS' BRIEF

APPEAL NO.:

ATTN: Board of Patent Appeals and Interferences
Commissioner for Patents and Trademarks
Washington, D.C. 20231

CERTIFICATE OF MAILING UNDER 37 CFR § 1.8(a)

I hereby certify that this paper (along with any referred to as being attached or enclosed) is being deposited with the U.S. Postal Service with sufficient postage as express mail in an envelope addressed to the: Assistant Commissioner of Patents, Washington, D.C. 20231, on November 15, 1999.

By: Linda P. Collins
Linda P. Collins

Sir or Madam:

This Appeal Brief is in furtherance of the Notice of Appeal Mailed on September 9, 1999, and received in the Mail Room on September 13, 1999.

The fees required under § 1.17(h) and any required Petition for Extension of Time for filing this Appeal Brief and fees therefore are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF.

This Appeal Brief is transmitted in triplicate. [37 CFR § 1.192(a).]

This Appeal Brief contains these items under the following headings and in the order set forth below [37 CFR § 1.192(c)]:

I. REAL PARTY IN INTEREST

The real party in interest is the assignee, Case Western Reserve University, of Cleveland, Ohio.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to Appellants or to Appellants' legal representative.

III. STATUS OF CLAIMS

Claims 1-17 were originally filed in the present Application. During prosecution of this Application, Claims 18-25 were added, Claims 4-8, 10-18, and 20-24 were withdrawn from consideration, and Claims 3, 9, and 19 were cancelled. Therefore, Claims 1, 2, and 25 are pending and have been rejected by the examiner. Appellants appeal the Final Rejection dated June 9, 1999.

The claims, as they now stand, are set forth in Appendix A (attached at Tab A).

IV. STATUS OF AMENDMENTS

Appellants have amended Claims 2 and 25 in the accompanying Amendment pursuant to 37 C.F.R. 1.116. Appellants appeal the claims as amended.

V. SUMMARY OF INVENTION

The present invention relates to methods for selectively inducing immunity, and in particular for inducing immunity that is protective against autoimmunity. The method

employs Selective Th Response Inducing Adjuvants (SThRIA). SThRIA are defined functionally as those adjuvants which induce either a Th1 response or a Th2 response upon administration. The present invention also relates to methods of screening for T helper 1 (Th1) Response Inducing Adjuvants (Th1RIA) and T helper 2 (Th2) Response Inducing Adjuvants (Th2RIA). (Specification, pg 3, lines 19-25).

In accordance with the present invention, immunity to protein antigens in adult humans is achieved by their injection of an Autoimmune Target Antigen (ATA). The ATA is part of an immunizing preparation comprising Incomplete Freund's Adjuvant (IFA). While it is not intended that the present invention be limited by the mechanism by which protective immunity is achieved, nor to the Th2RIA used, it is believed that the use of IFA induces unipolar T helper 2 (Th2) type immunity (*i.e.*, a Th2RIA), as opposed to the immunization with Complete Freund's Adjuvant (CFA), which triggers unipolar T helper 1 (Th1) type immunity. (CFA is a Th1RIA). The resistance to autoimmune disease that develops following injection of the ATA in IFA is a consequence of immune deviation, not tolerance in the immunological sense. (Specification, pg 3, line 26 - page 4, line 9).

The present invention provides a method of immunizing an adult human, comprising: a) providing: i) an adult with symptoms of autoimmune disease, and ii) an immunizing preparation comprising an Autoimmune Target Antigen and a Th2 Response Inducing Adjuvant; and b) immunizing said adult with said immunizing preparation under conditions such that said symptoms are reduced. The present invention also contemplates inducing protective immunity in adult humans by immunization with MBP in Incomplete Freunds Adjuvant. (Specification, pg 10, lines 25-26).

In another embodiment, the method further comprises: c) obtaining a primary cell population from said immunized adult comprising T cells capable of secreting cytokines; d) adding said primary cell population to said microwell comprising a hydrophobic membrane having a first cytokine binding ligand, under conditions such that said T cell secretes a cytokine that binds to said first cytokine binding ligand; and e) detecting said secreted T cell cytokine. (Specification, pg 4, lines 16-21)

In one embodiment of the method of the present invention, said Th2 Response Inducing Adjuvant is Incomplete Freund's Adjuvant. In another embodiment, said adult has symptoms of multiple sclerosis and said Autoimmune Target Antigen is myelin basic protein. (Specification, pg 4, line 4 - page 5, line 1). In another embodiment, said adult has symptoms of multiple sclerosis and said Autoimmune Target Antigen is proteolipid protein (PLP). (Specification, pg 4, lines 1-2).

VI. ISSUES

There are two issue involved with this appeal. The first is whether Claims 1 and 25 are patentable over Namikawa *et al.* in view of Tobin *et al.* (U.S. Pat. No. 5,674,978) and the prior art disclosed in the Specification (Alvord *et al.*, Zamvil *et al.*, and Kimball) under 35 U.S.C. 103. The second issue is whether Claims 1, 2, and 25 are patentable over Namikawa *et al.* in view of Tobin *et al.* (U.S. Pat. No. 5,674,978), the prior art disclosed in the Specification (Alvord *et al.*, Zamvil *et al.*, and Kimball), Goodwin *et al.* (U.S. Pat. No. 5,569,585), and Oprandy (U.S. Pat. No. 5,200,312).

VII. GROUPING OF CLAIMS

Each claim stands alone. Each claim has separate limitations and must be considered independently.

Independent Claim 1 specifies immunizing a human with myelin basic protein and Incomplete Freund's Adjuvant such that the immunization is protective against multiple sclerosis. Dependent Claim 2 further comprises obtaining a primary cell population from the immunized human comprising T cells capable of secreting cytokines, adding said primary cell population to a microwell comprising a hydrophobic membrane having a first cytokine binding ligand, and detecting said secreted T cell cytokine. This claim is not limited to a certain cytokine binding ligand, but it does require that the microwell comprises a hydrophobic membrane.

Independent Claim 25 specifies immunizing a human, having symptoms of multiple sclerosis, with proteolipid protein and Incomplete Freund's Adjuvant under conditions such that said symptoms are reduced.

Because each of the claims have different limitations, they do not stand or fall together. Rather, they need to be evaluated separately.

VIII. ARGUMENT

A. No *Prima Facie* Case of Obviousness is Established For Claims 1 and 25

The Examiner has rejected Claim 1 and 25 under 35 U.S.C. §103(a) as being unpatentable over Namikawa *et al.* (*J. of Immun.* 128: 932-934, February 1982) in view of Tobin *et al.* (US Pat. 5,674,978) and prior art disclosed in the Specification (Alvord *et al.*, Zamvil *et al.*, and Kimball). Applicants respectfully appeal this rejection.

The combination of references referred to by the Examiner fails to provide a *prima facie* showing of obviousness as required by §2143 of the Manual of Patent Examining Procedure (MPEP). There are three criteria which must be met to provide *prima facie* obviousness. The first of these is a suggestion or motivation in the references or the knowledge generally available to combine the reference teachings. The second is the prior art must teach or suggest all the claim limitations. The third is a reasonable expectation of success should the combination be carried out. Applicants submit that the Examiner has failed to set forth a *prima facie* case of obviousness because the combination does not teach all the claim limitations, there is no motivation to combine, and there is no reasonable expectation of success if the art is combined.

i. No Motivation Exists to Form This Combination

No motivation exists to combine these references as suggested by the Examiner. To establish a *prima facie* case of obviousness, "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference teachings." MPEP §2143.

The Examiner points to the references themselves in an attempt to establish a motivation for combining the references. Specifically, the Examiner combines the cited art stating, "Namikawa *et al.* teach that immunization with MBP in IFA prevents EAE in rats... " and "[o]ne of ordinary skill in the art would have been motivated to ... [form the claimed invention] ... because Tobin *et al.* teach treatment with autoimmune antigens for the treatment of human disease." (Office Action, pg 3).

While the Examiner continues to assert the Namikawa reference, it cannot be disputed that the Namikawa reference lacks any specific teaching regarding treatment of 1) humans with autoimmune symptoms (such as is claimed in Claim 25) and 2) humans to protect them against autoimmune disease. When one reads the discussion section of the Namikawa paper, one sees no suggestion to extend the work to humans - indeed, no suggestion that the work described in the paper has any particular application to prevention or treatment of autoimmune disease!

Similarly, while the Examiner continues to assert the Tobin reference, the Tobin reference is concerned with GAD and does not teach immunization with MBP. Tobin *et al.* discusses treating Insulin-dependent diabetes mellitus (IDDM) with glutamic acid decarboxylase (GAD) peptides, not treating multiple sclerosis with MBP in IFA.

How then does the Examiner justify the combination? Why would one skilled in the art combine the teachings of these disparate references?

In the Final Rejection, the Examiner states "the motivation to combine is reasoned from the knowledge generally available to one of ordinary skill in the art and established scientific principles." (Office Action, pgs 3-4). And yet, the Examiner does not describe what this general knowledge is or where it comes from, and does not point to anything in the record to provide the motivation. As such, since no motivation exists to combine the prior art references cited by the Examiner, no *prima facie* case has been established and Claims 1 and 25 should be allowed.

In regards to Claim 25, no motivations exists to modify Namikawa *et al.* as suggested by the Examiner. In particular, Namikawa *et al.* does not mention; 1. treating multiple sclerosis in humans, 2. treating a human with symptoms of multiple sclerosis, or 3. employing

proteolipid protein with IFA. The Examiner does not cite any other references which teach or suggest treating a subject for autoimmune disease (let alone multiple sclerosis) where the subject already has symptoms of the disease. Furthermore, the Namikawa *et al.* reference teaches away from using other central nervous tissue proteins, stating "[a]lthough whole CNS tissue can induce EAE in rats in the absence of mycobacteria, *i.e.*, in incomplete Freund's adjuvant (IFA) ... BP in IFA is a relatively weak encephalitogen in that species." (Namikura, *et al.*, pg 932, col. 1). In other words, Nakimura *et al.* suggests that other CNS tissue proteins (*e.g.* proteolipid protein) cause EAE in IFA. As such, this reference teaches away from employing proteolipid protein in IFA to treat multiple sclerosis as in Claim 25 because it suggests this combination would **cause** the disease, not **prevent** it. Consequently, the Examiner has failed to establish a *prima facie* case of obviousness, and Claim 25 should be allowed.

ii. No Reasonable Expectation of Successfully Combining the Art Exists

In order to establish a *prima facie* case of obviousness the prior art must, when combined, lead to a reasonable expectation of successfully producing the invention. MPEP § 2143.02. Applicants submit that one of ordinary skill in the art would not reasonably expect to produce the claimed invention by combining the cited references.

The Examiner combines Namikawa *et al.* and Tobin *et al.* to purportedly arrive at the claimed invention. (Office Action, pg 1-5). However, where is the teaching in the art that the experiments with GAD in the Tobin reference can be extended to any other autoimmune disease? Why would one of ordinary skill in the art have had a reasonable expectation of

success using MBP/IFA to protect humans from multiple sclerosis - when the Tobin reference is silent concerning MS?

It appears that the Examiner, using hindsight gained from a reading of the present specification, has genericized the Tobin reference teachings beyond the boundaries of the four corners of the Tobin patent. There is clearly no basis for doing so. Indeed, the confusing results of the Namikawa reference teach against such a generic approach. More specifically, Namikawa reports that MBP/IFA treated animals can transfer EAE!

In the present Office Action, the Examiner addresses this problem with Namikawa by arguing that the claims do not involve the transfer of cells from an immunized donor. This argument by the Examiner misses the point. The rejection is not a 102 rejection - it is a 103 rejection. The rejection is based on a combination of art - a combination which cannot be made without justification! Under law, the Examiner must examine the reference *as a whole* to determine what it teaches to one skilled in the art. It is submitted that the transfer experiments teach one skilled in the art that the *results* of treatment with MBP/IFA are **not** clear. Indeed, anyone who reads the discussion section of the Namikawa paper will understand that the authors are unable to explain the seemingly discrepant results - *thus raising the question as to whether the results can be relied upon!*

Since the results are not clear in the Namikawa reference, the Examiner cannot use it as justification to broaden the teachings of the Tobin reference. Since there is no other reference of record, no *prima facie* case of obviousness is established and Claims 1 and 25 should be allowed.

Finally, in regards to Claim 25, another reason no expectation of success exists is the fact that Nakimura *et al.* actually teaches away from using other CNS tissue proteins as

immunogens (*e.g.* PLP). Instead, Nakimura indicates that administering other CNS tissue proteins like PLP would actually cause EAE, instead of preventing its development (Namikura *et al.*, pg 932, col. 1). As such, no reasonable expectation of success exists to modify or combine the art cited by the Examiner. Consequently, no *prima facie* case of obviousness has been established, and Claim 25 should be allowed.

iii. The Combined Art Does Not Teach All of the Claim Elements

In order to establish a *prima facie* case of obviousness, the combined art must suggest or teach all of the Claim elements. MPEP 2143.03. Applicants submit the combined art fails to teach treating multiple sclerosis in humans with IFA and MBP or PLP. The Examiner cites Tobin *et al.* for treating autoimmune disease in humans, but this reference does not mention multiple sclerosis (as required in Claims 1 and 25). Furthermore, this reference does not suggest or teach treating any autoimmune disease where the patient already has symptoms of the disease as required by Claim 25. Finally, the Examiner has not cited a reference which teaches the administration of PLP with IFA as required by Claim 25. As such, the Examiner has failed to establish a *prima facie* case of obviousness.

B. No *Prima Facie* Case of Obviousness is Established For Claims 1, 2, and 25

The Examiner has rejected Claims 1, 2, and 25 under 35 U.S.C. §103(a) as being unpatentable over Namikawa *et al.* in view of Tobin *et al.*, the prior art disclosed in the Specification (Alvord *et al.*, Zamvil *et al.*, and Kimball), and further in view of Goodwin *et al.* (U.S. Pat. 5,569,585) and Oprandy (U.S. Pat. 5,200,312). The Examiner incorporates the above rejection of Claims 1 and 25, and focuses the present rejection on Claim 2. As such,

Applicants incorporate the above arguments by reference, and address the rejection of Claim 2 below. Applicants respectfully traverse this rejection because the Examiner has failed to establish the requirements of a *prima facie* case of obviousness.

No motivation exists to combine the cited references as suggested by the Examiner. To establish a *prima facie* case of obviousness, "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference teachings." MPEP §2143.

The Examiner combines Namikawa *et al.* and Goodwin *et al.* in an attempt to yield the present invention. In an effort to establish a motivation to combine these references, the Examiner points to the cell proliferation assay in Namikawa *et al.*, modifying it to produce a cytokine binding assay by combining Goodwin *et al.* The Examiner justifies this stating "[t]he response of T cells would have been alternatively measured using art known lymphokine assays, **because** the art recognizes that activated T cells produce lymphokines in response to antigenic stimulation... ". (Office Action, pg 5). The mere fact that the prior art may be modified in the manner suggested by the Examiner, however, does not make the modification obvious unless the prior art suggested the desirability of the modification. *In re Fritch*, 23 USPQ 2d 1780, 1783–84 (Fed. Cir. 1992). In this case, Namikawa *et al.* does not suggest why the cytokine production of T cells would be desirable. Namikawa *et al.* does not even mention measuring cytokines. The fact that Goodwin *et al.* describes a cytokine binding assay for activated T cells can be performed, does not provide the motivation why one skilled in the art would run this assay on the MBP/IFA activated cells of Namikawa *et al.* As such no motivation to combine is established and this rejection should be withdrawn.

Appellants submit that, with due consideration to all these factors discussed above, the patentability of the claims is evident. For the foregoing reasons, it is submitted that the examiner's rejections of Claims 1, 2, and 25 were erroneous, and reversal of these rejections is respectfully requested.

Dated: November 15, 1999

Peter G. Carroll
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IX. APPENDIX A: APPEALED CLAIMS

1. A method of immunizing a human, comprising:

a) providing: i) a human, and ii) an immunizing preparation comprising myelin basic protein and Incomplete Freund's Adjuvant; and

b) immunizing said human with said immunizing preparation under conditions such that said immunization is protective against multiple sclerosis.

2. The method of Claim 1, further comprising the steps of:

c) obtaining a primary cell population from said human comprising T cells capable of secreting cytokines;

d) adding said primary cell population to said microwell comprising a hydrophobic membrane having a first cytokine binding ligand, under conditions such that said T cell secretes a cytokine that binds to said first cytokine binding ligand; and

e) detecting said secreted T cell cytokine.

25. A method of immunizing a human, comprising:

a) providing: i) a human with symptoms of multiple sclerosis, and ii) an immunizing preparation comprising proteolipid protein and Incomplete Freund's Adjuvant; and

b) immunizing said human with said immunizing preparation under conditions such that said symptoms are reduced.

PATENT
Attorney Docket No. CASE-02138

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Paul V. Lehmann *et al.*
Serial No.: 08/621,725
Filed: 03/21/96
Entitled: **METHODS FOR INDUCING IMMUNITY**

Group No.: 1644
Examiner: R. Schwadron

TRANSMITTAL OF APPEAL BRIEF (PATENT APPLICATION - 37 CFR § 192)

Assistant Commissioner for Patents
Washington, D.C. 20231

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8(a)(1)(i)(A)

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being deposited with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

Dated: November 15, 1999 By: Linda P. Collins
Linda P. Collins

Sir or Madam:

1. Transmitted herewith, in triplicate, is the APPEAL BRIEF in this application, with respect to the Notice of Appeal filed on **September 9, 1999** and received in the Mail Room on **September 13, 1999**.

2. **STATUS OF APPLICANT**

This application is on behalf of

a small entity.

A verified statement has already been filed.

3. **FEE FOR FILING APPEAL BRIEF**

Pursuant to 37 CFR § 1.17(g), the fee for filing the Appeal Brief is:

Fee for Filing Appeal Brief $150.00

4. **EXTENSION OF TERM**

The proceedings herein are for a patent application and the provisions of 37 CFR § 1.136 apply.

Applicant believes that no extension of term is required. However, this conditional petition is being made to provide for the possibility that applicant has inadvertently overlooked the need for a petition and fee for extension of time.

5. **AMENDMENT UNDER 37 C.F.R. 1.116**

This amendment is being filed along with the appeal brief.

6. **TOTAL FEE DUE**

The total fee due is:

Appeal brief fee $150.00

Extension fee (if any) $0.00

TOTAL FEE DUE $150.00

7. **FEE PAYMENT**

Attached is a check for **$150.00**.

8. **FEE DEFICIENCY**

If any additional fee is required, charge Account No. **08-1290**.

Dated: November 15, 1999

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